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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,161	08/17/2001	Olivier Civelli	P-UC 4679	5376

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EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	7

DATE MAILED: 04/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,161	CIVELLI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *16-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-15* is/are rejected.

7)☒ Claim(s) *11 and 12* is/are objected to.

8)☒ Claim(s) *1-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application, Amendments and/or Claims

The information disclosure statement filed 07 December 2001 (Paper No. 3) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 24 May 2002 (Paper No. 4) has been entered in full.

Applicant's election with traverse of Group I (claims 1-10 and 13) in Paper No. 6 is acknowledged. The traversal is on the grounds that a search and examination of the entire application would not pose a serious burden on the Examiner.

Applicant's arguments have been considered and deemed partly persuasive. Applicant states that the specification teaches that determining the ability of a compound to promote wakefulness or sleep (claim 1b, 16b) involves an *in vivo* assay (specification, page 43, lines 5-8). The Examiner will rejoin Groups I-III (claims 1-15) and Groups IV-VI (claims 16-33).

Applicant states that the claims of Groups I and IV are directed to methods that involve providing a compound that modulates a PrRP receptor (agonists or antagonists) in a mammal. Because the claims all recite the same receptor and involve determining the ability of a compound to modulate a biological activity of this receptor, a search of the claims of Group I would include relevant art to the claims of Group IV. Applicant's arguments have been considered, but not deemed persuasive. There is no reason to believe that a search for a stimulant and a search for a soporific would be co-extensive. Groups I and IV each require divergent literature searches. The instant methods involve

administering diverse compounds (agonists and antagonists) and ascertaining different results. The requirement is still deemed proper and is therefore made FINAL.

Claims 16-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

Claim Objections

Claims 11 and 12 are objected to for depending on a rejected claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting wakefulness in a mammal, comprising administering to a mammal an effective amount of **PrRP**, does not reasonably provide enablement for a method of promoting wakefulness in a mammal, comprising administering to a mammal an effective amount of **PrRP receptor agonist**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure. The specification fails to teach a method of promoting wakefulness in a mammal, comprising administering to a mammal an effective amount of PrRP receptor agonist. The specification only teaches a method of promoting wakefulness in a mammal, comprising administering to a mammal an effective amount of PrRP. PrRP receptor agonist encompasses any biological equivalent, derivative or variant of PrRP. The specification does not disclose working examples demonstrating that any PrRP receptor agonist can promote wakefulness in a mammal. The specification (page 24) discloses alanine scanning mutagenesis of PrRP 25-31 (protein consisting of amino acid residues 25-31), however, this disclosure provides no guidance as to which regions in the core region of PrRP protein would be tolerant of modification and which would not. The specification discloses literature which demonstrates that various PrRP mutants can bind the PrRP receptor and stimulate calcium mobilization, but this is an *in vitro* assay. Most importantly, the specification does not teach or provide working examples of any variant sequence which would be within the claims (having the activity of promoting wakefulness in a mammal).

It is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of

antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517). It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any modified polypeptide could be used in the same manner as the native exemplar.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity of promoting wakefulness in a mammal, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for a method of promoting wakefulness in a mammal, comprising administering to a mammal an effective amount of PrRP, but not administering PrRP receptor agonists.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of PrRP, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides having the activity of promoting wakefulness in a mammal, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. None of these sequences meet the written description provision of 35 USC 112, first paragraph. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only PrRP but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that

Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 15 is rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al. Society for Neuroscience Abstracts, 1999. The instant claim is drawn to a method of promoting wakefulness in a mammal, comprising administering to a mammal an effective amount of a PrRP receptor agonist.

Zhang teaches the administration of PrRP to rats. Rats were implanted with EEG and EMG electrodes to discern the ability of PrRP to affect sleep regulation. Zhang demonstrates that at high doses, PrRP enhanced nonREM sleep with febrile responses in rats.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.* Society for Neuroscience Abstracts, 1999 in view of Curran *et al.*, US Patent No. 6,323,177 B1. The instant claims are drawn to a method of screening for a compound for promoting wakefulness in a mammal comprising; providing a compound that is a PrRP receptor agonist and determining the ability of said compound to promote wakefulness. The teachings of Zhang *et al.* are described above in the 102(a) rejection. Zhang does not teach methods of screening for compounds.

Curran teaches the interaction between reelin and the very low density lipoprotein (VLDL) receptor. Curran teaches assays of screening for agonists and antagonists (abstract). Curran teaches that a cell based assay can be used to screen for a few or large numbers of peptides or chemical compounds for their ability to modulate the binding of reelin to the VLDL receptor. Curran teaches very large libraries can be constructed to screen for agonists and antagonists (column 20, line 54-column

21, line 67). Curran teaches methods for detecting signals. Curran teaches screening assays where the predetermined signal is tyrosine phosphorylation or gene expression using reporter genes (column 23, lines 36-64).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention to include methods of screening for a compound for promoting wakefulness in a mammal, comprising providing a compound that is a PrRP receptor agonist and determining the ability of said compound to promote wakefulness. The motivation and expected success is provided by Zhang and Curran. Zhang demonstrates that PrRP, upon administration, enhances nonREM sleep. Zhang demonstrates this effect in rats. Zhang uses EEG and EMG measurements to determine sleep patterns. PrRP binds and activates the PrRP receptor. Curran teaches methods of screening for agonists and antagonists. Based on these teachings, it would be obvious to one skill in the art to be motivated to screen for other PrRP receptor agonists.

Claims 2-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.* Society for Neuroscience Abstracts, 1999 and Curran *et al.*, US Patent No. 6,323,177 B1 and further in view of Roland *et al.*, Endocrinology, 1999 (IDS submitted by Applicant, Paper No. 3). The teachings of Zhang *et al.* and Curran *et al.* are described above. Zhang and Curran do not teach methods where identifying a compound promotes predetermined signals such as calcium ion mobilization.

Roland teaches PrRP binds PrRP receptor (GP10) and stimulates calcium mobilization in CHOK1 cells transfected with PrRP receptor (page 5737, 2nd paragraph; page 5738, 3rd paragraph). Roland screened other PrRP receptor agonists for binding, competitive binding with PrRP, and calcium mobilization (page 5738, 2nd-3rd paragraph, Figures 2-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify to include a step which comprises contacting a PrRP receptor with more one or more candidate compounds under conditions wherein PrRP promotes a predetermined signal, and identifying a compound that promotes the predetermined signal. The motivation and expected success is provided by Roland and Curran. Roland demonstrates that PrRP, the natural ligand for PrRP receptor, binds and induces a signal of calcium mobilization. Roland tests other compounds for agonistic activity using the signal of calcium mobilization. Curran teaches methods for screening a large number of candidate compounds for agonistic and antagonistic activity. Based on these facts, it would be obvious for one skilled in the art to use this assay as a way to screen other PrRP receptor agonists.

Conclusion

Claims 11 and 12 are objected to.

Claims 1-10, 13-15 are rejected.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

RMD
March 27, 2003